

# COMPARISON OF EFFECTIVENESS OF MELOXICAM 15 MG ONLY, COMBINATION OF MELOXICAM 15 MG AND TAMSULOSIN 0.4 MG, AND TAMSULOSIN 0.4 MG ONLY FOR SUCCESS OF TWOC IN BPH PATIENTS WITH FIRST EPISODE OF ACUTE URINARY RETENTION

<sup>1</sup>Muhammad Asro Abdih Yasa, <sup>1</sup>Doddy M. Soebadi, <sup>1</sup>Fikri Rizaldi.

<sup>1</sup>Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

## ABSTRACT

**Objective:** To prove that Meloxicam 15 mg only, combination of Meloxicam 15 mg and Tamsulosin 0.4 mg were more effective for the success of Trial Without Catheter (TWOC) in BPH patients with first episode of urinary retention compared to Tamsulosin 0.4 mg only. **Material & methods:** Benign Prostatic Hyperplasia (BPH) patients with first episode of urinary retention that met the inclusion criteria and did not fulfill the exclusion criteria were randomized to form 3 treatment groups, n=11 for each group. Group I was given Meloxicam 15 mg only, group II was given a combination of Meloxicam 15 mg and Tamsulosin 0.4 mg, and group III was given Tamsulosin 0.4 mg only. For each group the drug given once orally for 7 days. The success of TWOC assessed by an ability to spontaneous micturition after that each treatment in the first 24 hours after urethral catheter removal, accompanied by  $Q_{max}$  in uroflowmetry  $\geq 5$  cc/sec and PVR  $\leq 100$  cc. **Results:** All Meloxicam 15 mg only group samples have recurred urinary retention (100%). The success rate of TWOC for combination of Meloxicam 15 mg and Tamsulosin 0.4 mg group was 72.7%; while for the Tamsulosin 0.4 mg only one was 63.6%. The success rate of TWOC for combination of Meloxicam 15 mg and Tamsulosin 0.4 mg group was higher than Tamsulosin 0.4 mg only one ( $p=0.003$ ). **Conclusion:** The combination of Meloxicam 15 mg and Tamsulosin 0.4 mg orally once daily for 7 days was more effective in the success of TWOC in BPH patients with first episode of urinary retention compared to Tamsulosin 0.4 mg only orally once daily for 7 days.

**Keywords:** Trial without catheter, Meloxicam, Tamsulosin, combination, Benign Prostatic Hyperplasia, urinary retention, first episode.

## ABSTRAK

**Tujuan:** Untuk membuktikan pemberian Meloxicam 15 mg saja, pemberian kombinasi Meloxicam 15 mg dan Tamsulosin 0.4 mg lebih efektif dalam keberhasilan Trial Without Catheter (TWOC) pada pasien BPH yang mengalami episode pertama retensi urine dibandingkan dengan pemberian Tamsulosin 0.4 mg saja. **Bahan & cara:** Pasien Benign Prostatic Hyperplasia (BPH) yang mengalami episode pertama retensi urine yang memenuhi kriteria inklusi dan tidak memenuhi kriteria eksklusi dilakukan randomisasi sehingga terbentuk 3 kelompok perlakuan. n=11 untuk masing-masing kelompok. Kelompok I diberikan Meloxicam 15 mg saja, kelompok II diberikan kombinasi Meloxicam 15 mg dan Tamsulosin 0.4 mg, dan kelompok III diberikan Tamsulosin 0.4 mg saja. Untuk masing-masing kelompok obat diberikan per-oral sekali sehari selama 7 hari. Dinilai keberhasilan TWOC yaitu kemampuan berkemih secara spontan setelah dilakukan perlakuan pada 24 jam pertama paska pelepasan kateter urethra, disertai dengan  $Q_{max}$  pada uroflowmetri  $\geq 5$  cc/detik dan PVR  $\leq 100$  cc. **Hasil:** Semua sampel kelompok Meloxicam 15 mg saja mengalami insiden retensi urine ulang (100%). Angka keberhasilan TWOC kelompok kombinasi Meloxicam 15 mg dan Tamsulosin 0.4 mg sebesar 72.7%; sedangkan kelompok Tamsulosin 0.4 mg saja adalah 63.6%. Tingkat keberhasilan TWOC kelompok kombinasi Meloxicam 15 mg dan Tamsulosin 0.4 mg lebih tinggi dibandingkan dengan kelompok Tamsulosin 0.4 mg saja ( $p=0.003$ ). **Simpulan:** Pemberian kombinasi Meloxicam 15 mg dan Tamsulosin 0.4 mg peroral sekali sehari selama 7 hari lebih efektif dalam keberhasilan TWOC pada pasien BPH yang mengalami episode pertama retensi urine dibandingkan dengan pemberian Tamsulosin 0.4 mg saja peroral sekali sehari selama 7 hari.

**Kata kunci:** Trial without catheter, Meloxicam, Tamsulosin, kombinasi, Benign Prostatic Hyperplasia, retensi urine, episode pertama.

Correspondence: Muhammad Asro Abdih Yasa, c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital. Jl. Mayjend. Prof. Dr. Moestopo 6-8, Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Mobile phone: 081553002619. Email: asroabdih@gmail.com.

**INTRODUCTION**

The prevalence of Benign Prostatic Hyperplasia (BPH) is 253 per 1000 population.<sup>1</sup> In above 50 years group, its incidence increased 10% per decade of age and reached 80% in men in their 80 years.<sup>2</sup>

Prostate inflammation implies the etiology and pathogenesis of BPH through static factors (prostate enlargement) and dynamic factors (smooth muscle contraction). Destruction of stromal and glandular prostate elements by proinflammatory cells causes tissue damage and produces prostate volume enlargement. BPH patients accompanied by prostate inflammation have large prostate volumes, severe LUTS, and a high tendency for urinary retention.<sup>3,4</sup>

Acute Urinary Retention (AUR) is defined as a sudden inability to spontaneous micturition with suprapubic pain.<sup>5</sup> The incidence of AUR in BPH patients was 44%.<sup>6</sup> Stimulation of the  $\alpha$ -adrenergic receptor and sympathetic nerve activity increase in smooth muscle contraction in the prostate and its capsule, and both theoretically will cause AUR.<sup>7-9</sup>

Trial Without Catheter (TWOC) is a procedure to evaluate whether patients can urinate spontaneously. The patient performs uroflowmetry test following removal of the catheter and a residual urine volume measurement after administration of  $\alpha$ -blockers drug for 3-7 days. It is done for first episode of urinary retention when the definitive diagnosis not yet defined.<sup>6,10</sup>

Inflammation which characterized by destructive infiltration of proinflammatory cells in glandular and stromal prostate is found in 55% of BPH patients with AUR.<sup>11</sup> Cyclooxygenase-2 (COX-2) inhibi-

tors can reduce and stop the inflammatory process in the prostate. Celecoxib, Tenoxicam, and Meloxicam has been studied for refractory nocturia complaints and LUTS in BPH patients. They increase IPSS, IPSS-Quality of Life (IPSS-QoL), and Overactive Bladder Symptom Score (OABSS). They also increase a maximal flow rate (Qmax).<sup>12-14</sup>

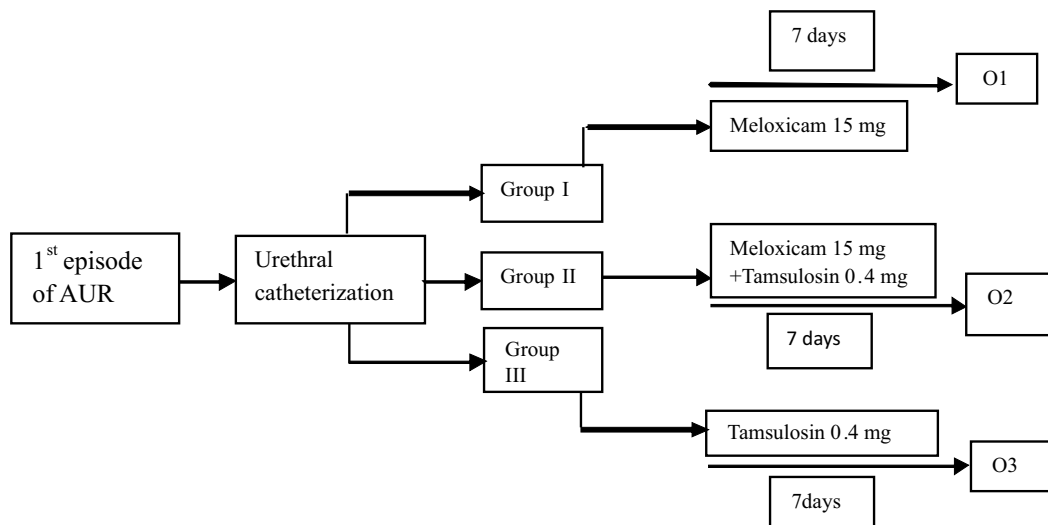
Recently there are limited even no study using Meloxicam or other COX-2 drug for the TWOC procedure. It is necessary to perform a study that proves whether Meloxicam only and combination of Meloxicam and Tamsulosin more effective than Tamsulosin only for success of TWOC in BPH patients with first episode of urinary retention.

**OBJECTIVE**

To prove that Meloxicam 15 mg only, combination of Meloxicam 15 mg and Tamsulosin 0.4 mg were more effective for the success of TWOC in BPH patients with first episode of urinary retention compared to Tamsulosin 0.4 mg only.

**MATERIAL & METHODS**

During October 2016 and March 2017, BPH patients with first episode of urinary retention in Soetomo General Hospital Surabaya that met the inclusion criteria and did not fulfill the exclusion criteria were included in this study. The inclusion criteria are a first episode of urinary retention caused by prostate enlargement confirmed by digital rectal examination, age > 50 years, and willing to follow the study. The exclusion one are 1) allergy to Non-



Picture 1. Design study.

Steroid Antiinflammatory Drugs (NSAIDs), 2) history of gastritis, based on anamnesis revealed a pain or burning sensation in the epigastrium, nausea, vomiting, and/or bloating; 3) disorder of liver function, be evidenced by elevated serum transaminase levels, 4) history of chronic kidney disease or elevated creatinine serum levels, 5) received  $\alpha$ -blocker, COX-2 inhibitor or drugs causing urinary retention such a decongestant or antiinfluenza in last 2 weeks, 6) history of uncontrolled diabetes mellitus over the past year, 7) history of surgery on the prostate (open or endoscopic), and 8) diagnosed as prostate cancer based on pathological examination.

The samples randomized into 3 treatment groups. n=11 for each group. Group I was given Meloxicam 15 mg only, group II was given a combination of Meloxicam 15 mg and Tamsulosin 0.4 mg, and group III was given Tamsulosin 0.4 mg only. The drugs given once orally for 7 days for each group.

TWOC performed by removal of urethral catheter after the treatment and followed by uroflowmetry test (Qmax), prostate volume and PVR measurement by abdominal sonography in the first 24 hours after it. The success of TWOC is defined as a spontaneous micturition with Qmax  $\geq$  5 cc/second

and PVR  $\leq$  100 cc.

Prostate volume and Intravesical Prostatic Protrusion (IPP) defined as confounding factor and its effect to success of TWOC analyzed by Kruskal-Wallis Test. The success rate of TWOC in each group was analyzed by Chi-Square test, considering a significant different if p value < 0.05. Data processed and analyzed by Statistical Package for the Social Sciences (SPSS) version 20 program.

## RESULTS

A total of 33 patients were included in the study. Each group consisted of 11 patients. Group I received Meloxicam 15 mg only, group II received a combination drugs (Meloxicam 15 mg and Tamsulosin 0.4 mg), and group III received Tamsulosin 0.4 mg only. Table 1 showed a baseline characteristics.

The prostate volume and IPP seem not interfere to the success of TWOC. Table 2 showed the statistical analysis.

Based on the statistical analysis, there were significant differences of success rate of TWOC in each group (p < 0.05) (Table 3). The success rate of TWOC was higher in the combination group. Compared to both the combination group and the

**Table 1.** Baseline characteristics of patient.

	Meloxicam 15 mg	Meloxicam 15 mg & Tamsulosin 0.4 mg	Tamsulosin 0.4 mg
Age (year)*	64.18 $\pm$ 8.90	59.64 $\pm$ 6.84	65.09 $\pm$ 6.73
Prostate volume (cc)*	43.00 $\pm$ 18.47	54.54 $\pm$ 13.46	52.41 $\pm$ 23.03
IPP (cm)	0 – 2.10	0 – 2.10	0 – 2.20
Micturition			
Spontaneous	3 (27.3%)	9 (81.8%)	9 (81.8%)
Recurred urinary retention	8 (72.7%)	2 (18.2%)	2 (18.2%)
Range of PVR (cc)	0 – 71.00	0 – 49.00	0 – 81.4
Range of Qmax (cc/sec)	0 – 3.40	0 – 8.00	0 – 12.8
Range of Void volume (cc)	0 – 128.00	0 – 112.00	0 – 156.9

**Table 2.** Comparison of volume and IPP in each group.

	Meloxicam 15 mg	Meloxicam 15 mg & Tamsulosin 0.4 mg	Tamsulosin 0.4 mg	p value
Volume (cc)*	38.00 (24.50–78.00)	56.30 (27.80–69.80)	46.20 (27.1–93.7)	0.20
IPP (cm)*	0.30 (0–2.10)	0.40 (0–2.10)	0.50 (0–2.2)	0.59

**Table 3.** The success rate of TWOC in each group.

Groups	TWOC				p value
	Success		Failure		
	n	%	n	%	
Meloxicam 15 mg	0	0	11	100	0.003*
Meloxicam 15 mg and Tamsulosin 0.4 mg	8	72.7	3	27.3	
Tamsulosin 0.4 mg	7	63.6	4	36.4	
Total	15	45	18	55	

**Table 4.** The effectiveness of each groups to Qmax.

Groups	n	Median	Min	Max	p value
Meloxicam 15 mg	11	0	0	3.40	0.002*
Meloxicam 15 mg & Tamsulosin 0.4 mg	11	5.60	0	8.00	
Tamsulosin 0.4 mg	11	5.90	0	12.80	

Tamsulosin 15 mg only, the Meloxicam 15 mg only group did not have effect for success of TWOC.

When post hoc analysis was used to compare the differences between each group for increasing Qmax, it also showed that the Meloxicam 15 mg only group had the lowest effect ( $p < 0.05$ ). It mean that Meloxicam did not have any effect for Qmax (Table 4).

## DISCUSSION

AUR was an important problem that causes a bothersome in elderly men. As a complication, AUR was associated with BPH. Catheterization, a procedure to decompress the bladder, was the first action performed in the event of AUR and subsequently followed by immediate surgery. However, immediate surgery has a higher morbidity and mortality rate than elective surgery. This lead to drive TWOC as a gold standard management and applied in many countries for AUR associated with BPH particularly in first episode.<sup>6,15</sup>

The use of alpha-blockers have known to cause a success of TWOC for BPH patients with AUR. Bowden et al and Lucas et al reported a higher success of TWOC after of alpha-blockers administration compared to placebo, that was 63% and 37%, 33.8% and 24.3% subsequently. Alpha-blockers was to be useful for AUR and LUTS associated with BPH by decreasing sympathetic tone, reducing bladder outlet resistance, and facilitate to spontaneous micturition.<sup>16,17</sup>

Tuncel et al reported a high incidence of AUR in BPH patients with prostatic inflammation. The inflammation, which ranged from mild to

severe and identified by destructive infiltration of proinflammatory cells in glandular and stromal element of the prostate, was found in 55% BPH patients with AUR. The inflammation will cause an edema, destruction, and prostatic infarction. The edema results in higher prostate volume. The high volume and prostatic infarction were another risk factor for BPH to be AUR.<sup>7-9,11</sup>

Since the discovery of the relationship between BPH and inflammatory processes, the use of NSAIDs in LUTS management has been widely studied. A meta analytic study by Kahokehr et al showed a positive effect of NSAID in lowering LUTS caused by BPH. They concluded that there were an improvement of LUTS (IPSS: International Prostate Symptom Score and IPSS Quality of Life), OABSS (Overactive Bladder Symptom Score), and increasing of Qmax without significant side effects after administration of NSAID.<sup>18,19</sup> Di Silverio et al have reported that the combination of finasteride and rofecoxib was better than single-finasteride therapy in reducing LUTS in patients with BPH.<sup>20</sup>

Gorgel et al. have reported that the combination of Meloxicam and Tamsulosin was better than single-tamsulosin therapy only in reducing LUTS caused by BPH.<sup>21</sup> Similarly, Suarsana et al also reported that combination therapy of Meloxicam 15 mg and Doxazosin 4 mg once daily orally for 6 weeks was better in increasing Qmax in BPH patients with LUTS.<sup>14</sup>

The results of this study were similar to all the studies explained above. The highest success rate of TWOC was shown in the combination group. The combination of Meloxicam 15 mg and Tamsulosin 0.4 mg can improve spontaneous micturition,

Qmax, and decrease of PVR. It can be noted that the highest success rate of TWOC in combination group might be due to the synergistic effect between Meloxicam and Tamsulosin. The ability of Meloxicam in inhibiting COX-2 was thought to play an important role. Several studies have shown that high COX-2 expression and prostaglandins can cause partial obstruction of the bladder outlet due to high volume of the prostate and the mechanism of action of Tamsulosin in reducing sympathetic tone in bladder outlets and prostate stroma might play a major role in the success of TWOC.<sup>20,22-24</sup>

This study also showed that Meloxicam 15 mg only has the lowest success rate compared to the other groups for TWOC. It postulated that AUR for the first episode in patients with BPH may be due to predominance of sympathetic tone activity rather than inflammation. It also likely due to the effects of NSAIDs which can lead to urinary retention.

The inhibitory effect of COX-2 enzyme by NSAID in the bladder will cause a decrease in prostaglandin synthesis and this lead to impaired bladder contraction resulting AUR. Verhamme et al found that the risk of AUR was 2.02 times higher in NSAID users than people who did not use.<sup>25</sup> Therefore, it needs further investigation to prove the dominance of the sympathetic factor compared to acute or chronic inflammation in pathophysiology of AUR in BPH patient.

## CONCLUSION

The combination of Meloxicam 15 mg and Tamsulosin 0.4 mg orally once daily for 7 days was more effective in the success of TWOC in BPH patients with first episode of AUR compared to Tamsulosin 0.4 mg only orally once daily for 7 days. Meloxicam only had the lowest effect for success of TWOC and did not have any effect for Qmax.

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